IN THE SPECIFICATION

Please amend the specification in accordance with the following proposed amendments. The amendments proposed herein are not believed to add any new matter, particularly in view of MPEP § 2163.07(a) which provides that "[b]y disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent applicant necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter," citing *In re Reynolds*, 443, F.2d 384, 170 USPQ 94 (CCPA 1971). *See also*, *Ex Parte Davisson*, 133 USPQ 400 (Pat. Off. Bd. App. 1958) where the Examiner entered an amendment reciting optical rotation data and elemental analysis of the sulfate of a claimed substance including the spectroscopic characteristics of the claimed substance. The Examiner regarded this information as inherent properties of material adequately disclosed in the specification of the application.

Applicant's amendments are further supported by MPEP § 2163.07(a), and by 2163.07(I. Rephrasing), (II. Obvious Errors), and typographical errors.

Please replace the paragraph beginning at page 4, line 23 with the following amended paragraph:

Figure 1 is a graphic representation of the concentration of butorphanol in blood plasma versus time ~~for two different butorphanol formulations~~ after administration of the test formulation from a unit-dose spray device (Invention) and the administration of the test formulation in a multi-dose spray device (Prior Art).

Please replace the paragraph beginning at page 5, line 14 with the following amended paragraph:

In accordance with one embodiment of the present invention, it has now been surprisingly found that intranasal pharmaceutical compositions can be made having improved bioavailability in terms of plasma opioid levels. These intranasal compositions contain an opioid; and a liquid nasal carrier for the opioid. For example, it has been unexpectedly discovered, among other things, that at least about 10 to about 20% higher plasma levels of butorphanol can be achieved by administering an intranasal formulation ~~that does not contain the preservative benzethonium~~ <u>from a unit-dose spray device</u>. ~~Thus, butorphanol formulations without benzethonium have improved bioavailability due to improved nasal absorption of butorphanol.~~ Improved bioavailability includes increases in plasma or serum opioid concentration when compared to prior art opioid formulations. Preferred increases include, but are not limited to, increases of more than 5% to ~~more than~~ 40% in bioavailability of the opioid.

Please replace the paragraph beginning at page 7, line 6 with the following amended paragraph:

In some embodiments of the present invention, the composition contains a preservative that is chosen in quantities that preserve the composition, but do not cause irritation of the nasal mucosa. Suitable preservatives for use in some embodiments of the present invention include, but are not limited to, benzalkonium chloride, methyl, ethyl, propyl or butylparaben, benzyl alcohol, phenylethyl alcohol, benzethonium, or combination thereof. Typically, the preservative is added to the compositions of the present invention in quantities of from about 0.01% to about 0.5% by weight. ~~However, in some embodiments of the present invention, the inclusion of benzethonium has been found to reduce bioavailability. For example, it has been unexpectedly discovered that at least about 10 to about 20% higher plasma levels of butorphanol can be achieved by administering an intranasal composition that does not contain the preservative benzethonium. Thus, butorphanol formulations without benzethonium have improved bioavailability due to improved nasal absorption of butorphanol.~~

Please replace the paragraph beginning at page 12, line 16 with the following amended paragraph:

The examples below demonstrate improved bioavailability of ~~the preferred~~ illustrative compositions of the present invention ~~as~~ when delivered from a unit-dose spray device compared to the ~~prior art pharmaceutical~~ same compositions when delivered from a multi-dose spray device. The examples also show pharmaceutical compositions that include sweeteners, flavoring agents, or masking agents or combinations thereof, which can improve patient compliance.

Please replace the paragraph beginning at page 12, line 22 with the following amended paragraph:

This example compares bioavailability of a butorphanol formulation when administered using a unit-dose or multi-dose delivery device. ~~of the present invention to prior art butorphanol for intranasal administration sold commercially by Bristol Myers Squibb under the trademark STADOL®NS. The lml of STADOL®NS (reference formulation)~~ The formulation contains 10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0. The ~~prior art formulation is~~ multi-dose sprayer ~~that~~ purports by its label to administer 0.1 ml of liquid composition by metering upon activation by the user. The formulation had the following function and properties when administered to human subjects via the Pfeiffer Unitdose Second Generation spray device. Administration of a 2 mg dose of butorphanol tartrate produced a T_{max} (hr) of about 0.234 (range about 0.083 to about 0.333); a C_{max} (pg/ml) of about 5230 (range of about 2393 to about 8478); an $AUC_{(0-t)}$ of about 10661 pg*hr/ml (range of about 5351 to about 17722). Administration using the multi-dose spray pump produced a T_{max} of 0.245 hr, a C_{max} of 4072 pg/ml and a $AUC_{(0-t)}$ of 9329 pg*hr/ml.

Please replace the paragraph beginning at page 13, line 3 with the following amended paragraph:

~~The butorphanol composition (test formulation), in one embodiment of the present invention, contains 10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg anhydrous citric acid in purified water with 1 N sodium hydroxide and/or 1 N hydrochloric acid added to adjust the pH to 5.0. The butorphanol test formulation did not contain benzethonium chloride.~~ The second delivery system employed to administer [[~~one of~~]] the butorphanol compositions ~~of the present invention~~ was a unit-dose disposable intranasal applicator that is commercially available from Pfeiffer of America under the designation "Unitdose Second Generation." Each of the Pfeiffer spray applicators was charged with sufficient liquid to deliver a 0.1 mL dose of the butorphanol test formulation ~~without the benzethonium chloride~~. The glass containers were filled using a pipette under clean conditions, sealed and assembled to the applicator. Each of the applicators was weighed prior to use and after use. Qualified medical personnel administered ~~to the respective applicators to patients in a clinical setting from the drug had been prescribed and attended each of the patient's self administration~~, one dose [[~~up~~]] into each nostril, after which the applicator was recovered for weighing. In the case of the unit-dose applicators, ~~each patient used~~ two devices were used for each patient, both of which were discarded following the post-use weighing. The results of these studies of the method and system of the invention and the comparative prior art method follow:

Please replace the paragraph beginning at page 14, line 18, with the following amended paragraph:

The F test for the comparison of variances revealed that the variability in the total doses dispensed by the multi-dose sprayer ~~(reference formulation)~~ was significantly higher than the variability in weights dispensed by the unit-dose sprayer ($F = 18.7$; $p < 0.001$). The variability in

the multi-dose sprayer is 18.6 times that of the unit-dose sprayer ~~(test formulation)~~. High variability in dose delivery leads to higher rates of adverse drug effects at excessive dose and inadequate treatment if the dose is low. Both consequences harm the patient hence the goal is to precisely deliver the prescribed dose.

Please replace the paragraph beginning at page 15, line 6, with the following amended paragraph:

Bioequivalence

This example assesses the bioequivalence of a ~~two different~~ butorphanol formulation[[s]] administered from the unit-dose or multi-dose sprayers described above. The test ~~reference~~ formulation ~~is~~ comprises 1ml of STADOL [[®~~NS~~]] NS® containing 10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg citric acid, 0.20 mg benzethonium chloride in purified water with 1.2 mg sodium hydroxide and hydrochloric acid added to adjust the pH to 5.0. The multi-dose sprayer used to administer accompanying STADOL [[®~~NS~~]] NS® purports, by its label, to administer 0.1 ml of liquid. ~~The test formulation contains 10 mg butorphanol tartrate, 6.5 mg sodium chloride, 1.0 mg anhydrous citric acid in purified water with 1N sodium hydroxide and/or 1N hydrochloric acid added to adjust the pH to 5.0. The butorphanol test formulation did not contain benzethonium chloride.~~ The unit-dose delivery device ~~for the test formulation~~ delivers 0.1 ml of liquid.

Please replace the paragraph beginning at page 15, line 18, with the following amended paragraph:

The second analysis was to determine whether the intrasubject variabilities of the two ~~formulations~~ spray devices are equal. The study was initiated with 16 subjects, 15 of which

completed the study to provide data for this analysis; one subject dropped out after the second period. The following analysis considers both raw and normalized data, with the latter standardized with respect to the dose dispensed.

Please replace the paragraph beginning at page 16, line 7, with the following amended paragraph:

The mean levels of butorphanol from analysis of the subject's blood plasma reported in pg/ml [[~~is~~]] <u>are</u> plotted against time in Figures 1 and 2. The concentration of drug for the <u>unit-dose system</u> ~~test formulation~~ was unexpectedly higher than that of the <u>multi-dose system</u> ~~reference formulation~~. The testing for bioequivalence was done using the method of two one-sided t-test (as described by Bolton, S., *Pharmaceutical Statistics*. Marcel Dekker, Inc., New York, 1997, pages 415 ff.). For each parameter, the 90% confidence interval for the ratio of the test unit-dose to reference multi-dose <u>devices</u> ~~formulations~~ appear in Table 2 below.

Please replace the paragraph beginning at page 16, line 18 and ending on page 17, line 7, with the following amended paragraph:

Since none of these confidence intervals for the non-standardized data are contained in the interval from 0.8 to 1.25, the conclusion is that the two ~~formulations~~ <u>devices</u> (test and reference) are not equivalent when compared on raw values. For T_{max}, the one-sided t-test for H_0: Test/Reference <0.8 is not rejected. Also, the tests of H_0: Test/Reference >1.25 are not rejected for any of the log-transformed raw values. While the normalization by dispensed doses does improve the comparability of the two <u>devices</u> ~~formulations~~, two of the three parameters fail to reject the null hypothesis H_0: Test/Reference >1.25. Bioequivalence is supported only by the

pair of one-sided tests for the normalized, log-transformed AUC(inf). Both one-sided t-test for each of the seven parameters have been performed at an alpha level of 0.05.

Please replace the paragraph beginning at page 17, line 9, with the following amended paragraph:

The data show[[s]] that the ~~an unexpectedly high degree of non-bioequivalence for an~~ FDA-approved ~~formulation~~ (STADOL [[®~~NS~~]] NS®) product that has been sold and dispensed for a number of years unexpectedly delivers below label strength. The degree of ~~non-equivalence~~ variability is also significantly greater than that of the method of the invention using the Pfeiffer device. Since the test formulation administered from the unit-dose device achieves higher drug serum concentration, the small excess in unit-dose administration can be further reduced by adjusting the volume and/or drug concentration placed in the delivery device. Thus, the drug container can actually be filled with less drug.

Please replace the paragraph beginning at page 17, line 18, with the following amended paragraph:

The Pitman-Morgan adjusted F test was used to compare variances of the unit-dose and multi-dose parameters. (See Chow, S-C. and Liu, J-P, *Design and Analysis of Bioavailability and Bioequivalence Studies*. Marcel Dekker, Inc., New York (2000)). Since this test could not be generalized to the three period design, the first two periods of the butorphanol trial were used, and for the purposes of this analysis, there are two delivery devices ~~formulations~~, two periods, and two sequences. The Pitman-Morgan adjusted F test can be used even if the period effect is significant, and has a simplified form in the absence of period effects. Of the seven PK parameters considered, only T_{max} exhibited a significant period effect. Table 3 summarizes the

results of the tests of equality. The null hypothesis is that the variances are equal, and small p-values are indicative of a departure from equality.

Please replace the paragraph beginning at page 18, line 3, with the following amended paragraph:

The tests of equality variances indicate that for all PK parameters except Tmax, the variabilities of the two dose systems ~~formulations~~ are significantly different,[[,]] with the unit dose system demonstrating much lower variability of drug levels in the blood. While the normalization of the C_{max}, AUC(last) and AUC(inf) parameters somewhat decreased the difference between the variances (as evidenced by slightly smaller F values), the variances were nonetheless significantly different. The variability associated with the unit-dose system was smaller than that of the multi-dose system of the prior art, which is consistent with the findings of the delivery volume weight study.

Please replace the paragraph beginning at page 18, line 12, with the following amended paragraph:

From the above, it is apparent that the dose weight/volume data is confirmed by the blood level (pharmacokinetic) analysis. The ~~reference~~ formulation administered from the multi-dose device results in an area under the curve that is 90% of the test formulation of the present invention. Thus, the test ~~formulation~~ device achieves 10% higher area under the curve and 10% higher serum levels as compared to the reference ~~formulation~~ device. This difference is highly significant from a patient therapy standpoint. When FDA-prescribed bioequivalence statistical methods are applied, it is concluded that-the products as administered to the patients are not equivalent. Thus, the unit-dose device ~~butorphanol test formulation~~ in one embodiment of the

present invention provides an unexpected improvement in the intranasal administration of butorphanol.

Please insert the following new paragraphs, which describe the function of the device and formulations disclosed herein, beginning at page 19, line 8, before Example 2.

The formulation substantially as described immediately above was prepared but did not contain benzethonium chloride. This formulation had the following spray pattern function when sprayed from the Pfeiffer Unitdose Second Generation device onto an impaction plate from at various distances. At a spray distance of 1 cm the spray had an average maximum diameter (D_{max}) of about 2.3 cm (range 2.2 – 2.4), an average minimum diameter (D_{min}) of about 2.1 cm (range 2.0 – 2.2) and an average ovality of about 1.1 (range of 1.0 to 1.2; 9.1% RSD). At a spray distance of 3 cm the spray had an average maximum diameter (D_{max}) of about 5.2 cm (range of 4.2 – 6.1), an average minimum diameter (D_{min}) of about 4.6 cm (range of 3.8 – 5.8) and an average ovality of about 1.1 (range of 1.0 – 1.3; 9.2% RSD). At a spray distance of 5 cm, the spray had an average maximum diameter (D_{max}) of about 7.9 cm (range of 7.0 – 8.4), an average minimum diameter (D_{min}) of about 7.2 cm (range of 5.8 – 8.0) and an average ovality of about 1.1 (range of 1.0 to 1.2; 6.6% RSD).

At a spray distance of 1 cm from a detection laser beam, the spray ha a droplet size distribution having a mean Dv10 of about 15.45 μm (range of 13.70 to 19.98), a mean Dv50 of about 41.46 μm (range of 35.74 to 55.67) and a mean Dv90 of about 93.88 μm (range of 69.55 to 117.15). The spray had a mean span [(Dv90-Dv10/Dv50)] of about 1.76 (range of 1.55 – 1.91).

At a spray distance of 3 cm, the spray had a droplet size distribution having a mean Dv10 of about 13.83 μm (range of 11.84 to 15.68), a mean Dv50 of about 35.29 μm (range of 29.46 to 41.69) and a mean Dv90 of about 90.80 μm (range of 71.2 to 122.42). The spray had a mean span [(Dv90-Dv10/Dv50)] of about 2.17 (range of 1.92 – 2.56).

At a spray distance of 5 cm, the spray had a droplet size distribution having a mean Dv10 of about 15.82 μm (range of 14.38 to 17.17), a mean Dv50 of about 32.96 μm (range of 31.03 to

35.32) and a mean Dv90 of about 71.85 µm (range of 61.64 to 83.68). The spray had a mean span [(Dv90-Dv10/Dv50)] of about 1.69 (range of 1.50 – 1.90).

The formulation had the following function and properties when administered to human subjects via the Pfeiffer Unitdose Second Generation spray device. Administration of a single 2 mg dose of butorphanol tartrate produced a T_{max} (hr) of about 0.25 (range 0.167 to about 0.5); a C_{max} (ng/ml) of about 2.08 to about 4.68; and an AUC$_{(0-t)}$ of about 7.6 to about 11.41 ng*hr/ml.

Please replace the paragraph beginning at page 19, line 11, with the following amended paragraph:

In accordance with the composition and methods described above, hydromorphone HCL (HM HCL) was formulated in a liquid composition for use in the practice of one embodiment of the invention. HM HCL is a potent mu-receptor ~~against~~ agonist opiate analgesic with properties similar to morphine. HM HCL is chemically similar to morphine, oxymorphone, and codeine and shares many of their analgesic and pharmacological properties.

Please replace the paragraph beginning at page 21, line 19, with the following amended paragraph:

Nine healthy male subjects between the ages of 22 and [[~~28~~]] 33 years participated in this inpatient study. Study participants were selected based on inclusion/exclusion criteria, history and physical exam, laboratory tests, and other customary procedures. Subject demographics were recorded. These included age range: 22-[[~~28~~]] 33 years; height range: 168~~175~~-188 cm; weight range: 70.3-95.3/kg; origin: six Caucasian, two Asian, one Native American; all were non-smokers. All nine of the subjects completed the study according to the protocol. Each of the subjects received 3 doses of 2 mg of HM HCL on three separate occasions. No clinically significant protocol violations occurred during this study. Because the inclusion criteria

mentioned abstinence from prescription and non-prescription drugs prior to and during the study, any medications taken in the 14 days before the. study and during the study were noted.

Please replace the paragraph beginning at page 22, line 16, with the following amended paragraph:

On days 1 and 8, 2.0 mg of HM HC1 was given intravenously or intramuscularly in random order following an overnight fast. On day 15, [[~~3.0~~]] 2.0 mg of HM HC1 was given intranasally following an overnight fast (except for water *ad lib*). Subjects were not permitted to recline for 4 hours following drug administration and remained fasting for 4 hours (until lunch) on these study days.

Please replace the paragraph beginning at page 23, line 7, with the following amended paragraph:

Blood samples for period I through period III were collected from each subject according to the following schedule: 0 (pre-dose), 5, 10, 15, 20, 30 and 45 minutes, and 1, 2, 3, 4, 6, 8, 12 and 16 hours following HM HC1 administration. The beginning of the IV administration was considered time zero. After collection, the blood was centrifuged in a refrigerated centrifuge at [[~~40°C~~]] 4 °C to separate the plasma and the cells and the plasma was transferred to polypropylene tubes. The plasma was stored at approximately [[~~-700°C~~]] 70 °C at the study site until shipped to an independent analytical service. The plasma was maintained frozen during shipping and upon arrival at the remote analytical facility, the samples were stored at approximately -20°C until analyzed.

Please replace the paragraph beginning at page 25, line 8, with the following amended paragraph:

Non-compartmental pharmacokinetic analysis was used to evaluate the plasma concentration versus time curves of hydromorphone following single 2.0 mg doses of hydromorphone HCL by intravenous (IV), intramuscular (IM), and intranasal (1N) routes. Individual plasma hydromorphone concentrations versus time profiles for all subjects were recorded; the number of time points used to estimate the elimination rate constant were also recorded; and a complete listing of individual and mean pharmacokinetic parameters for all 9 subjects was recorded. ~~Table 4.2 is a summary of the descriptive statistics for hydromorphone pharmacokinetic, parameters.~~

Please replace the paragraph beginning at page 26, line 3, with the following amended paragraph:

The pharmacokinetic parameters in Table [[~~4.3~~]] 4 were analyzed to evaluate the effect of routes of administration and to test for period and sequence effects. The analysis of this pilot data is considered in two parts: the first part considers only the first two periods and includes the factors of treatment, sequence (i.e., a test of carryover effects) and period; the second part contains all three periods and treatments, but ignores the effects of sequence and period. The 2-period analysis is noted in Table [[~~4.3~~]] 4 as period 1 vs. 2 and the last column contains the 3-period model.

Please replace the paragraph beginning at page 26, line 10, with the following amended paragraph:

There are even more significant treatment effects for these nine outcomes. Post-hoc analyses are based on Fisher's least significant difference procedure and displayed in Table [[~~4.3~~]] 4. In light of the fact that there were no significant period or sequence effects (using an alpha level of 0.05), and since this is a pilot project, it is arguable that the above analysis is appropriate.

Please replace Table 4 on page 27 with the following replacement Table 4.

Table 4 Summary of significance levels from IN 2-period and 3-period model

Parameter	**Sequence (1 vs 2)**	**Period (1 vs 2)**	**Treatment IV vs IM**	**Treatment (IV vs IM vs 1N)**
T_{max}	NS*	NS	NS	.0001
C_{max}	NS	0.32	0.71	.0001
C_{max}(omit outlier)	NS	[[~~0.32~~]] 0.62	NS	.0001
AUC_{0-t}	NS	NS	.0001	.0001
AUC_{0-oo}	NS	NS	.0001	.0001
$t_{½}$	NS	NS	NS	NS
CL/F	NS	NS	.0001	.0001
Dose	NS	NS	.0001	.0001
